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Prognostic and clinical implications of c-erbB-2 expression in patients with oral cancer

A meta-analysis

Ying Meng, MS, Peng Yang, BD, Lili Ma, MS*

Abstract

Background: Recently, many studies have suggested that the aberrant expression of c-erbB-2 existed in oral cancer (OC) patients and had a correlation with poor clinical features across OC patients. Considering the inconsistent results among published articles, we performed the meta-analysis to assess the prognostic and clinical effect of c-erbB-2 expression on oral tumors.

Methods: Web of Science, Embase, and PubMed were retrieved to acquire relevant publications based on selection criteria, up to February 8, 2020. Pooled odds ratios (OR) and hazard ratios (HR) with 95% confidence intervals (CI) were applied to evaluate the associations between c-erbB-2 expression and overall survival (OS), disease specific survival, disease-free survival as well as clinicopathology of OC.

Results: A total of 30 literatures with 1499 patients for survival of OC were enrolled in this meta-analysis. The results indicated that c-erbB-2 overexpression was significantly associated with poor OS (HR = 2.40, 95% CI = 1.53–2.55, $P < .05$), disease specific survival (HR = 2.60, 95% CI = 1.11–4.10, $P < .05$) and disease-free survival (HR = 2.22, 95% CI = 1.46–2.99, $P < .05$). Subgroup analysis based on race showed that the significant prognostic value of c-erbB-2 in OC was found both in Caucasians and Asians (OS of Caucasians, HR = 2.90, 95% CI = 1.50–4.31, $P < .05$; OS of Asians, HR = 1.90, 95% CI = 1.27–2.53, $P < .05$). Moreover, OC patients with enhanced c-erbB-2 expression were prone to male (OR = 1.97, 95% CI = 1.22–3.19, $P < .05$), advanced TNM stage (OR = 1.84, 95% CI = 1.17–2.88, $P < .05$), lymph node metastasis (OR = 2.23, 95% CI = 1.47–3.36, $P < .05$) and advanced grade (OR = 1.98, 95% CI = 1.30–3.01, $P < .05$), but not associated with distant metastasis (OR = 1.65, 95% CI = 0.98–3.04, $P > .05$).

Conclusions: c-erbB-2 may be a potential indicator in the prediction of prognosis and clinicopathological features in OC patients.

Abbreviations: CIs = confidence intervals, DFS = disease-free survival, DSS = disease specific survival, HRs = hazard ratios, IHC = immunohistochemistry, OC = oral cancer, ORs = odds ratios, OS = overall survival, OSCC = oral squamous cell carcinoma.

Keywords: c-erbB-2, meta-analysis, oral cancer, overexpression, prognosis

1. Introduction

Globally, oral cancer (OC) is the most frequent cancer of the head and neck district, approximately accounting for 2% of all cancer patients, with a nearly 50% mortality rate.[1] Published reports have found South Asian countries such as India, Sri Lanka, and Taiwan had the highest rates of OC.[2] Multiple factors including genetic factors and environmental factors contribute to the initiation of OC. Tobacco, alcohol, areca nut, and high-risk human papillomavirus infection have been identified as significant risk factors for OC.[3] In addition, specific germline mutations such as germline TP53 mutation, HOTAIR mutation, and NFKB1 mutation have also been associated with a higher incidence of OC.[4–6] The patients with dyskeratosis congenita have increased risk of OC because of defective telomerase maintenance.[7] In fact, oral squamous cell carcinoma (OSCC) accounts for large proportions of OC cases arising in the head and neck region.[8] Surgery and/or radiotherapy were commonly used to treat the OC patients with localized disease, which resulted to a better prognosis but with considerable morbidity.[9] Chemotherapy and radiotherapy are the mainstays of treatment for the OC patients with metastatic disease.[9] Recently, some targeted biological drugs such as cetuximab and bevacizumab, have been introduced into the treatment regimens of OC, which improved the quality of life in OC patients.[9] Although many therapeutic strategies have been discovered and developed in the field of OC treatment, the prognosis has not significantly improved over the past few decades.[10] Oral cancer patients with advanced stage often had a low response rate to current therapeutic strategies, which leaded to the poor prognosis. These patients were often diagnosed with advanced tumor stage, lymph

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The datasets generated during and/or analyzed during the current study are publicly available.

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node metastasis, distant metastasis, and high occurrence of invasion. Therefore, the discovery of new and valuable biomarkers which significantly associated with the risk and progression of oral tumor may be benefit for the treatment of OC.

The c-erbB-2/HER2/neu gene, locating at chromosome 17q21, encodes a 185 kD transmembranous receptor protein, which is a member of the EGFR/HER family and involved in proliferation, migration, invasion, and apoptosis of cells.[11,12] It has been reported that the level of c-erbB-2 protein had aberrant rise in cancer patients with early stage, thus c-erbB-2 might be a reliable biomarker for the initial diagnosis and screening of cancers. One study has detected c-erbB-2 protein expression in the tumor tissue of patients with OSCC, and the results demonstrated the levels of c-erbB-2 was significantly increased.[13] However, other researchers have found that there was no significant association between clinical features of OCs and c-erbB-2 expression.[14] Considering the diversity of oral tumor types, more detailed studies might be conducted based on OC types, race, clinical features, and other affecting factors such as gender. Therefore, we carried out the meta-analysis to analyze the potential value of c-erbB-2 protein expression in the prognosis and clinical progression of OC.

2. Methods

2.1. Search strategies

Literatures regarding the correlation between c-erbB-2 expression and OC were searched from Web of Science, Embase, and PubMed databases up to February 8, 2019. The following search terms: "oral cancer," "c-erbB-2," "HER2," "neu," "prognosis," "Salivary Gland Tumors," "Oral Squamous Cell Carcinoma," "Salivary mucoepidermoid carcinomas," "Oropharyngeal Squamous Cell Carcinoma," "Squamous cell carcinomas of the tongue," and "Salivary carcinoma ex pleomorphic adenoma" were used. Additionally, references of relevant articles were also browsed.

2.2. Selection of studies

All potential articles were assessed by 2 independent reviewers. All candidate articles had to meet the following inclusion criteria:

1. The OC patients of relevant articles should be diagnosed by histopathology;
2. c-erbB-2 expression in cancer tissue was detected with immunohistochemistry (IHC);
3. The article had to contain enough data to calculate hazard ratio (HR), odds ratio (OR), and 95% confidence intervals (CI); and
4. the studies were written in English. Moreover, any disagreement was resolved via discussion.

The exclusion criteria were as follows:

1. These articles were removed such as: reviews, letters, editorials, case-reports, and meta-analysis;
2. Duplicate and insufficient data;
3. Studies which were performed in animal specimens.

And Medical Ethics Committee of Liaocheng People's Hospital approved this study.

2.3. Data extraction and quality assessment

Two researchers independently extracted the following data: first author's name, publication date, race, OC type, detecting methods, number of cases and controls, HRs and 95% CI, cut-off value, and follow-up median time. Moreover, clinical information including histological classification, tumor stage (TNM), tumor grade, lymph node metastasis, and distant metastasis were extracted from the relevant articles.

We applied the Newcastle-Ottawa Scale to evaluate the quality of primary studies. According to the selection of the subjects, the comparability of cases and controls, and the ascertainment of the exposure, the included studies were scored. A study awarded 0 to 3, 4 to 6, or 7 to 9 was considered as a low, moderate, or high-quality study.

2.4. Statistical analysis

The association between c-erbB-2 expression and clinical features of OC was measured by OR with 95% CI. In addition, HR and 95% CI were extracted from included studies based on the methods described by Tierney et al.[15] Heterogeneity among the studies was assessed using Cochran Q test and I^2 statistics.[16] $P < .05$ or $I^2 > 50\%$ indicated a severe heterogeneity among relevant studies. If significant heterogeneity existed, the random effects model was used ($P < .05$ or $I^2 > 50\%$); otherwise, the fixed effects model was applied.[17] Begg test and egger test were conducted to evaluate the publication bias.[18] Finally, the sources of heterogeneity were investigated by performing a sensitivity analysis. All statistical analysis was conducted with STATA version 14.0 (STATA, College Station, TX).

3. Results

3.1. Characteristics of included studies

A total of 665 literatures were preliminarily identified from PubMed, Web of Science, and Embase electronic databases. After eliminating duplicate studies, 654 records remained. Then titles and abstracts of all the studies were read, and 546 articles were excluded. After carefully scanning the full texts, an additional 78 articles were removed. Furthermore, additional an article with insufficient data was eliminated. Ultimately, 29 eligible studies were eventually included in our meta-analysis[19–47] (Fig. 1). In these studies, 1499 OC patients were included to analyze the association between c-erbB-2 expression and survival of OC patients, while 188 controls and 254 cancer patients were recorded for the correlation of c-erbB-2 expression with OC risk. The characteristics of the 29 included studies is presented in Table 1, Table 2 and Supplementary Tables S1 to S5, http://links.lww.com/MD/E358, http://links.lww.com/MD/E359, http://links.lww.com/MD/E360, http://links.lww.com/MD/E361, http://links.lww.com/MD/E362. Among these eligible studies, 14 studies about overall survival (OS) were performed,[19–26,28,29,31–35] 2 studies on disease specific survival (DSS),[27,36] and 5 reports about disease-free survival (DFS).[19,28,33,35,36] In addition, 6 reports were performed to analyze the correlation between OC risk and c-erbB-2 expression, 7 studies for gender of subjects, 7 articles for tumor grade, 9 studies for lymph node metastasis, 6 reports for TNM stage, and 3 records for metastasis. All the OC patients of the eligible studies were in accordance with the clinical diagnostic criteria of OC.

3.2. Meta-analysis results

The association between c-erbB-2 overexpression and survival of OC was shown in Table 3. The results indicated that c-erbB-2 overexpression was significantly associated with OS, DSS, and

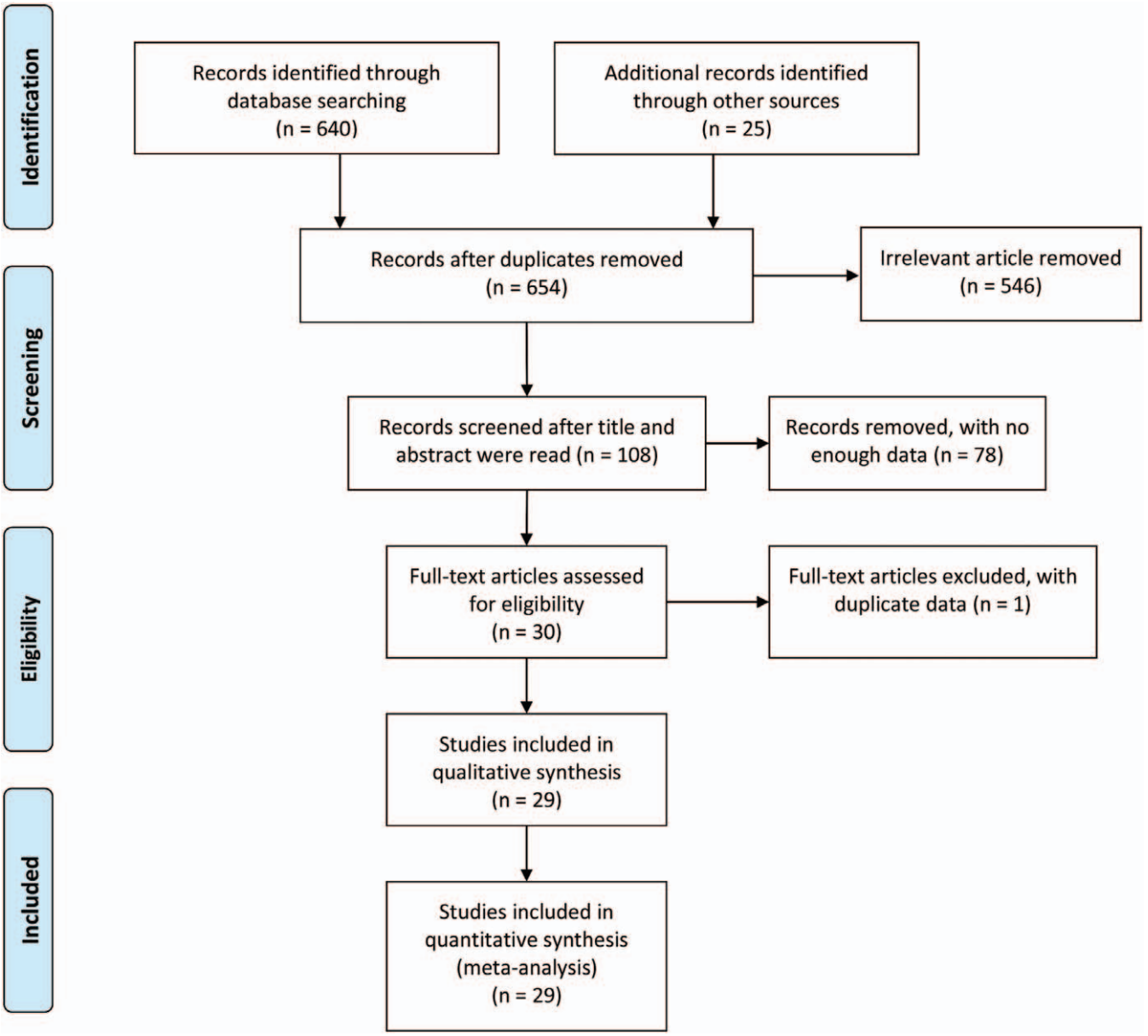

Figure 1. Flowchart of study section.

DFS of OC (OS, HR = 2.40, 95% CI = 1.53–2.55, $P < .05$; DSS, HR = 2.60, 95% CI = 1.11–4.10, $P < .05$; DFS, HR = 2.22, 95% CI = 1.46–2.99, $P < .05$). Significant heterogeneity was found in the preliminary analysis for OS of OC. Sensitivity analysis revealed that Masubuchi et al and Boon et al contributed to the mainly heterogeneity in Asians and Caucasians,[15,19] therefore, the 2 studies were removed in the finally meta-analysis. The results of subgroup analysis based on race and source of HRs suggested that significant correlation between c-erbB-2 expression and OS of OC was still found in Caucasians and Asians (OS in Caucasians, HR = 2.90, 95% CI = 1.50–4.31, $P < .05$; OS in Asians, HR = 1.90, 95% CI = 1.27–2.53, $P < .05$). Stratified analysis based on cancer type revealed that c-erbB-2 overexpression resulted to worse prognosis in salivary gland cancer (OS, HR = 2.45, 95% CI = 1.39–3.51, $P < .05$; DFS, HR = 2.44, 95% CI = 1.41–3.46, $P < .05$), OSCC (OS, HR = 4.27, 95% CI = 1.79–6.75, $P < .05$), and salivary mucoepidermoid carcinomas (OS, HR = 7.39, 95% CI = 1.59–13.19, $P < .05$), but not in squamous cell carcinomas of the tongue (OS, HR = 1.76, 95% CI = 0.94–2.57).

Six studies contributed data to the analysis of OC risk. No significant heterogeneity was found among eligible studies, and fixed effect model was used. The results demonstrated that c-erbB-2 overexpression significantly enhanced the risk of OC (OR = 9.99, 95% CI = 4.17–23.95, $P < .05$). In addition, significant correlations between c-erbB-2 overexpression and gender (OR = 1.97, 95% CI = 1.22–3.19, $P < .05$), TNM stage (OR = 1.84, 95% CI = 1.17–2.88, $P < .05$), lymph node metastasis (OR = 2.23, 95% CI = 1.47–3.36, $P < .05$) and advanced grade (OR = 1.98, 95% CI = 1.30–3.01, $P < .05$) of OC was found, but

Table 1

The main information of included studies in the meta-analysis for the oral cancer prognosis.

Author	References	Time	Country	Ethnicity	Method	Cancer type	Follow-up median	Survival analysis	Source of HR	HR	95%CI	*P*	Analysis type	Cut off
Sugano	19	1992	Japan	Asians	IHC	SGC	5 yr	OS	SC	1.48	1.02–4.90	.023	Univariate	0.33
Sugano	19	1992	Japan	Asians	IHC	SGC	5 yr	DFS	SC	2.74	1.45–8.49	.006	Univariate	0.33
Press	20	1994	USA	Caucasians	IHC	SMC	12.5 yr	OS	SC	8.42	2.52–16.35	.0011	Univariate	0.1
Giannoni	21	1995	USA	Caucasians	IHC	SGC	3.5 yr	OS	SC	3.03	1.47–5.27	.009	Univariate	NR
Xia	22	1997	China	Asians	IHC	OSCC	3.5 yr	OS	SC	5.47	2.85–12.64	.001	Univariate	NR
Kuropkat	23	2002	USA	Caucasians	IHC	OC	5 yr	OS	SC	3.22	1.06–10.29	.007	Univariate	0.01
Chen	24	2003	China	Asians	IHC	OC	3 yr	OS	HR	1.08	0.36–3.26	.888	Multivariant	NR
Weed	25	2004	USA	Caucasians	IHC	SMC	3 yr	OS	SC	4.95	1.09–22.4	.01	Univariate	0.1
Zhang	26	2004	China	Asians	IHC	SCCT	5 yr	OS	SC	1.87	1.06–3.31	.017	Univariate	0.1
Williams	27	2007	USA	Caucasians	IHC	SDC	5 yr	DSS	SC	2.04	0.93–5.28	.444	Univariate	0.5
Silva	28	2008	Brizal	Mixed	IHC	SCCT	5 yr	OS	SC	1.63	1.01–3.37	.0096	Univariate	NR
Silva	28	2008	Brizal	Mixed	IHC	SCCT	5 yr	DFS	SC	1.66	1.15–3.64	.0029	Univariate	NR
Silva	29	2009	Brizal	Mixed	IHC	OSCC	5 yr	OS	SC	3.86	1.93–7.68	.0005	Univariate	NR
Triantafillidou	30	2010	Greece	Caucasians	IHC	ACCMSG	5 yr	OS	SC	2.85	0.69–8.68	.477	Univariate	0.1
Ettl	31	2012	Germany	Caucasians	IHC	SGC	6 yr	DSS	SC	3.11	1.67–5.80	.008	Univariate	0.1
Cros	32	2013	France	Caucasians	IHC	SGC	NR	OS	HR	0.89	0.12–6.80	.91	Multivariant	0.1
Masubuchi	33	2014	Japan	Asians	IHC	SDC	2 yr	DFS	HR	1.33	0.17–10.43	.787	Univariate	0.1
Masubuchi	33	2014	Japan	Asians	IHC	SDC	2 yr	OS	HR	0.42	0.08–2.08	.288	Univariate	0.1
Xia	34	2016	China	Asians	IHC	SCEPA	5 yr	OS	HR	1.89	1.03–3.48	.04	Univariate	0.1
Hashimoto	35	2017	Japan	Asians	IHC	SGC	5 yr	DFS	HR	2.41	1.54–3.68	.001	Univariate	0.1
Hashimoto	35	2017	Japan	Asians	IHC	SGC	5 yr	OS	HR	3.37	1.89–5.82	.001	Univariate	0.1
Haderlein	36	2018	Germany	Caucasians	IHC	SDC	5 yr	DFS	SC	4.84	1.32–8.65	.04	Univariate	0.1
Boon	37	2018	Netherland	Caucasians	IHC	SDC	5 yr	OS	HR	1.08	0.65–1.81	.76	Univariate	NR

ACCMSG = Acinic Cell Carcinoma of Minor Salivary Glands, CIs = confidence intervals, DFS = disease-free survival, DSS = disease specific survival, HRs = hazard ratios, IHC = immunohistochemistry, NR = not reported, OC = oral cancer, OS = overall survival, OSCC = oral squamous cell carcinoma, SC = survival curve, SCCT = squamous cell carcinomas of the tongue, SCEPA = salivary carcinoma ex pleomorphic adenoma, SDC = salivary duct carcinoma, SGC = salivary gland cancer, SMC = salivary mucoepidermoid carcinomas.

not distant metastasis (OR = 1.65, 95% CI = 0.98–3.04, $P > .05$). We also performed subgroup analysis by ethnicity, and the results of subgroup analysis revealed that significant associations between c-erbB-2 overexpression and occurrence risk (Caucasians, OR = 10.39, 95% CI = 3.68–29.35, $P < .05$; Asians, OR = 9.00, 95% CI = 1.77–45.79, $P < .05$), gender (Caucasians, OR = 2.51, 95% CI = 1.16–5.41, $P < .05$; Asians, OR = 3.21, 95% CI = 1.34–7.70, $P < .05$), advanced grade (Caucasians, OR = 1.87, 95% CI = 1.07–3.26, $P < .05$; Asians, OR = 7.83, 95% CI = 2.32–26.39, $P < .05$), lymph node metastasis (Caucasians, OR = 2.85, 95% CI = 1.13–7.18, $P < .05$; Asians, OR = 2.15, 95% CI = 1.27–3.64, $P < .05$) of OC were identified. Furthermore, stratified analysis based on type of control group showed that c-erbB-2 overexpression significantly associated with OC risk in normal tissues (OR = 11.68, 95% CI = 4.29–31.78, $P < .05$) and benign tissues (OR = 6.77, 95% CI = 1.19–38.44, $P < .05$) (Figs. 2 and 3, Tables 3 and 4).

3.3. Publication bias and sensitivity analysis

In order to assess publication bias among published literatures, Begg and Egger test were conducted, and significant publication bias was not detected. The similar results were also found in the funnel plots, and the shapes of funnel plot appeared symmetrical. Finally, we conducted sensitivity analysis by removing each study to evaluate the impact of each study on the overall results. These results showed that no individual study had excessive effect on the stability of overall results. Therefore, the overall results were robust (Tables 3 and 4).

4. Discussion

IHC is the most attractive method to evaluate the level of some proteins due to low cost, convenience, and biological relevance. So many studies have been performed to assess the role of

Table 2

Characteristics of the included studies for the oral cancer risk.

							Control			Case				
Author	Reference	Time	Country	Ethnicity	Method	Histology	Sample type	c-erbB-2 -	c-erbB-2 +	Sample type	c-erbB-2 -	c-erbB-2 +	Cut-off	NOS
Hou	38	1992	USA	Caucasians	IHC	OC	Normal tissue	7	0	Tumor tissue	0	21	NR	6
Karja	39	1994	Finland	Caucasians	IHC	SGC	Benign tissue	75	41	Tumor tissue	77	36	NR	7
Giannoni	21	1995	USA	Caucasians	IHC	SGC	Benign tissue	16	1	Tumor tissue	26	16	NR	7
Wilkman	40	1998	Finland	Caucasians	IHC	OSCC	Benign tissue	6	0	Tumor tissue	10	1	0.1	7
Bei	41	2001	Italy	Caucasians	IHC	OC	Normal tissue	4	0	Tumor tissue	10	9	0.1	6
Fong	42	2008	China	Asisns	IHC	OSCC	Normal tissue	18	2	Tumor tissue	15	15	0.1	7
Seifi	43	2009	Iran	Caucasians	IHC	OSCC	Normal tissue	16	2	Tumor tissue	10	8	0.1	6

IHC = immunohistochemistry, NOS = Newcastle-Ottawa Scale, NR = not reported, OC = oral cancer, OSCC = oral squamous cell carcinoma, SGC = salivary gland cancer.

Table 3

Meta-analysis results for the associations of c-erbB-2 expression with OS of oral cancer.

Characteristics (Negative vs Positive)	Studies	Cancer type	Pooled HR (95% CI)	P	Heterogeneity I^2 (%)	Heterogeneity P	Begg test Z	Begg test P	Egger test T	Egger test P
OS	14	OC	2.40 (1.53–2.55)	<.05	2%	.436	0.38	.702	0.33	.743
OS in Caucasians	6	OC	2.90 (1.50–4.31)	<.05	0%	.547	−0.56	.573	−0.46	.669
OS in Asians	6	OC	1.90 (1.27–2.53)	<.05	10.80%	.347	−1.32	.188	−0.65	.553
OS (Source of HR)	4	OC	1.83 (1.01–2.65)	<.05	18.90%	.296	−1.36	.174	−1.62	.246
OS (Source of SC)	10	OC	2.18 (1.53–2.83)	<.05	1.5%	.425	0.98	.325	1.35	.213
OS	2	SCCT	1.76 (0.94–2.57)	>.05	0%	.773	–	–	–	–
OS	4	SGC	2.45 (1.39–3.51)	<.05	0%	.759	−1.36	.174	−1.67	.238
OS	2	OSCC	4.27 (1.79–6.75)	<.06	0.00%	.578	–	–	–	–
OS	2	SMC	7.39 (1.59–13.19)	<.07	0.00%	.592	–	–	–	–
DSS	2	OC	2.60 (1.11–4.10)	<.05	0%	.484	−1	.317	–	–
DFS	5	OC	2.22 (1.46–2.99)	<.05	0%	.548	0.49	.624	0.26	.814
DFS	2	SGC	2.44 (1.41–3.46)	<.05	0.00%	.86	–	–	–	–
DFS	2	SDC	3.65 (0.67–6.64)	>.05	16%	.275	–	–	–	–

CIs = confidence intervals, DFS = disease-free survival, DSS = disease specific survival, HRs = hazard ratios, IHC = immunohistochemistry, OC = oral cancer, OS = overall survival, OSCC = oral squamous cell carcinoma, SC = survival curve, SCCT = squamous cell carcinomas of the tongue, SDC = salivary duct carcinoma, SGC = salivary gland cancer, SMC = salivary mucoepidermoid carcinomas.

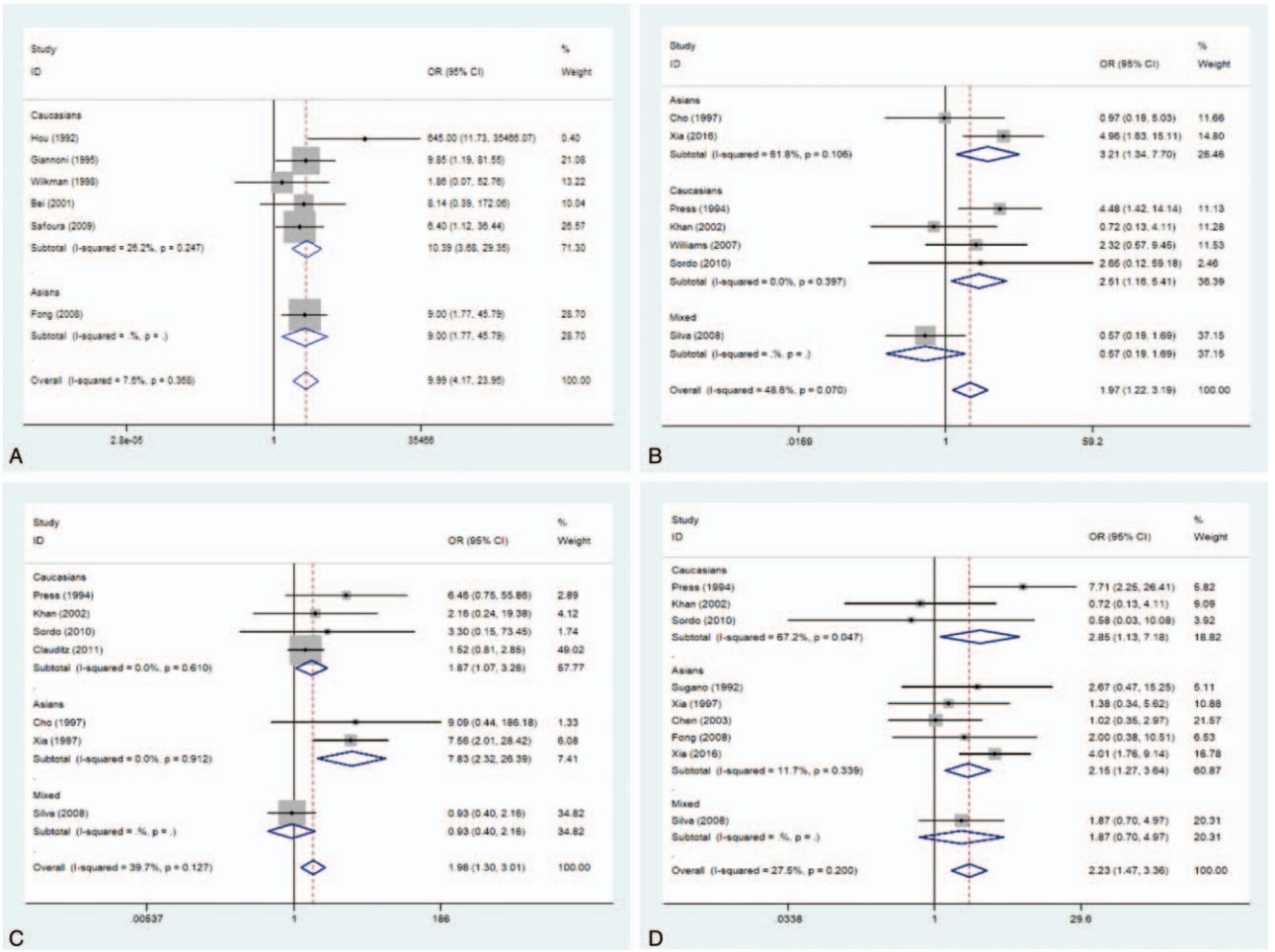

Figure 2. Forest plot of odds ratios for the association between high c-erbB-2 expression and clinicopathological parameter in oral cancer patients (c-erbB-2- vs c-erbB-2+). A, oral cancer risk; B, gender (female vs male); C, tumor grade; D, lymph node metastasis.

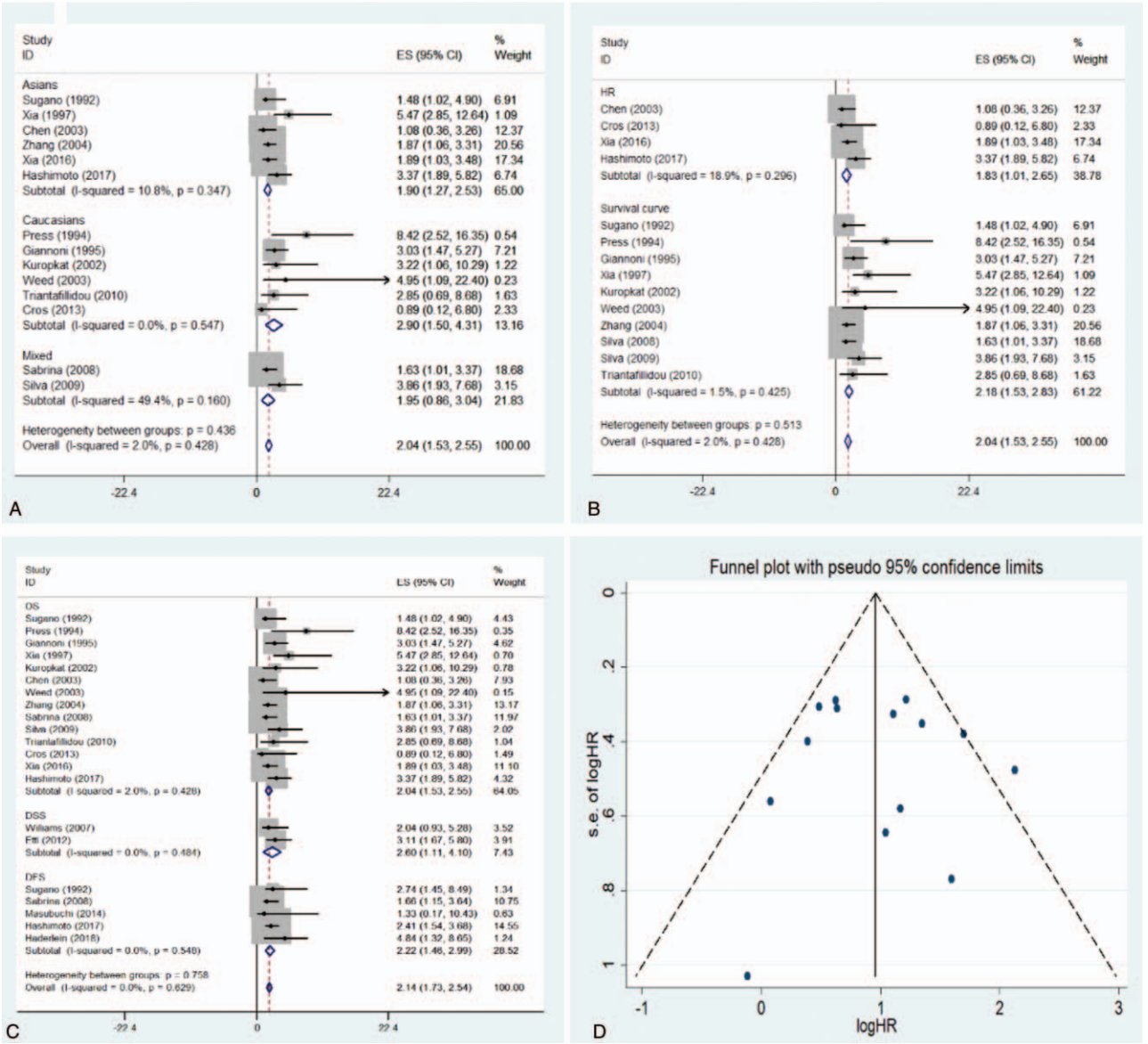

Figure 3. Forest plot and funnel plot for the association between high c-erbB-2 expression and survival of oral cancer patients (c-erbB-2- vs c-erbB-2 +). A, subgroup analysis based on ethnicity; B, subgroup analysis based on source of hazard ratio; C, subgroup analysis based on survival type; D, funnel plot of overall survival in oral cancer.

biomarkers expression in the prognosis and clinical progression of OC with IHC. The application of molecular markers has provided an effective approach in prediction of clinical outcome of OC. These immunohistochemical markers such as p53, Ki-67, and PCNA significantly correlated with histopathologic grade of OC.[48–50] However, some other markers such as Muc4, bcl-2, p27 correlated with histopathologic grade inversely.[25,51–52] Therefore, these proteins might contribute to different effects on the OC progression. Moreover, studies acquired contradictory results regarding association between c-erbB-2 expression and OC due to multiple factors like: age, sample type, gender, cut-off value, country, tumor histopathology, and tumor stage. A larger sample size may decrease the influence of these factors in the overall results, and stratified analysis is possible to be conducted to obtain more accurate results. Oral cancer contained many tumor subtypes such as: carcinoma of gingiva, tongue cancer, salivary gland carcinoma, and carcinoma of lip. Oral carcinoma can be divided into squamous cell carcinoma and adenocarcinoma based on cell morphology. So, identifying the histopathological type is crucial to investigate the association between c-erbB-2 expression and OC. Cetuximab, an inhibitor of EGFR receptor, is very effective to the treatment of OC patients especially those who cannot tolerate carboplatin.[53] As another receptor of the EGFR family, c-erbB-2/HER2 might have potential medical value in OC patients.

The overall results indicated that expression of c-erbB-2 was higher in OC tissues than that in normal tissues and benign tissues. Moreover, the similar result was detected both in Asians and Caucasians. No significant heterogeneity was found in the

Table 4

Meta-analysis of association between increased e-crebB-2 expression and clinicopathological parameters of oral cancer.

Characteristics (Negative vs Positive)	Studies	Pooled OR (95% CI)	P	Heterogeneity		Begg test		Egger test	
				I^2 (%)	P	Z	P	T	P
Risk (Overall)	6	9.99 (4.17–23.95)	<.05	7.6	.368	0.19	.851	0.87	.434
Risk (Caucasian)	5	10.39 (3.68–29.35)	<.05	26.2	.247	0.49	.624	0.87	.447
Risk (Asian)	1	9.00 (1.77–45.79)	<.05	–	–	–	–	–	–
Risk (Normal tissue)	4	11.68 (4.29–31.78)	<.05	32.8	.216	1.36	.174	1.7	.231
Risk (Benign tissue)	2	6.77 (1.19–38.44)	<.05	0	.405	–	–	–	–
Gender (Female vs Male)	7	1.97 (1.22–3.19)	<.05	48.6	.07	−0.75	.453	−0.34	.745
Gender (Caucasians) (Female vs Male)	4	2.51 (1.16–5.41)	<.05	0	.397	−0.68	.497	−0.7	.554
Gender (Asians) (Female vs Male)	2	3.21 (1.34–7.70)	<.05	61.8	.106	–	–	–	–
Tumor grade (Overall) (G1 vs G2+G3)	7	1.98 (1.30–3.01)	<.05	39.7	.127	0.45	.652	1.86	.121
Tumor grade (Caucasian) (G1 vs G2+G3)	4	1.87 (1.07–3.26)	<.05	0	.61	0.68	.497	1.96	.189
Tumor grade (Asian) (G1 vs G2+G3)	2	7.83 (2.32–26.39)	<.05	0	.912	–	–	–	–
Lymph node metastasis (Overall) (N0 vs N1)	9	2.23 (1.47–3.36)	<.05	27.5	.2	−0.83	.404	−1.24	.253
Lymph node metastasis (Caucasian) (N0 vs N1)	3	2.85 (1.13–7.18)	<.05	67.2	.05	−0.52	.602	−1.42	.391
Lymph node metastasis (Asian) (N0 vs N1)	5	2.15 (1.27–3.64)	<.05	11.7	.339	0.49	.624	−0.76	.5
TNM stage (Overall) (T1-T2 vs T3-T4)	6	1.84 (1.17, 2.88)	<.05	1.7	.406	0.56	.573	0.83	.452
TNM stage (Caucasian) (T1-T2 vs T3-T4)	2	3.12 (0.79, 12.28)	>.05	27.8	.239	–	–	–	–
TNM stage (Asian) (T1-T2 vs T3-T4)	3	1.45 (0.82, 2.58)	>.05	25.1	.263	0.52	.602	0.16	.901
Metastasis (No vs Yes)	3	1.65 (0.89–3.04)	>.05	0	.909	−0.52	.602	0.23	.856

CIs = confidence intervals, OR = odds ratio.

overall analysis and subgroup analysis. In published primary studies,[40,41] 2 studies found there was no significant association of c-erbB-2 expression with OC risk, and 6 records obtained positive results.[21,38,39,42,43] However, only 1 study has been conducted in Asians, thus more studies might be performed in Asians. To evaluate the value of c-erbB-2 expression in the clinical progression of OC, the meta-analysis was carried out to investigate the correlations between c-erbB-2 expression and gender, tumor grade, tumor TNM stage, and lymphatic metastasis. The results indicated that c-erbB-2 overexpression significantly promoted lymph node metastasis and tumor grade of oral tumor cells. Although significant association was observed in the overall analysis for tumor TNM stage, it was not detected in the subgroup analysis based on ethnicity. Additionally, the association preferred in male than female. No apparent heterogeneity was found, and sensitivity analysis suggested that these results were robust. And, these positive results were observed in Asians and Caucasians. Thus, c-erbB-2 overexpression leaded to the poor differentiation and lymphatic metastasis of oral tumor cells, which were consistent with the function of c-erbB-2 protein.[11,12] Potential clinical benefits of c-erbB-2 target treatment may be achieved in the adjuvant treatment for OC patients with lymph node metastasis and advanced grade. In a study regarding gastric cancer, Lei et al observed a significant correlation between c-erbB-2 expression and clinical outcome (TNM staging system, distant metastasis, lymph node metastasis, and differentiation grade) of gastric cancer patients.[54] Therefore, the significant association may not only exist in OC patients. However, this cannot obscure the therapeutic value of c-erbB-2 in OC, which can be demonstrated in the studies of EGFR receptor.

In addition, our pooled analysis revealed that c-erbB-2 overexpression had played a favorable role in the prognosis of OC. In subgroup analysis, c-erbB-2 overexpression was significantly associated with OS, DFS, and DSS of OC patients. The data of meta-analysis for patients' survival extracted from HRs or survival curve, which might lead to heterogeneity. However, in the stratified analysis based on source of HRs, significant correlation of c-erbB-2 overexpression with OS of OC patients was still observed and no significant heterogeneity was found. Although some included individual report found negative results,[6,12–14] significant association was detected in the overall results. As expected, Begg test and Egger test revealed that no publication bias existed, and no individual study affected the overall result. Therefore, c-erbB-2 expression might be a valuable biomarker for prognosis of OC patients.

It should be noted that several limitations still exist in the report. First, the cut-off value of IHC varied in studies. However, the cut-off value of lots studies was 10%. Second, although many studies were included for the meta-analysis, the studies were still few after subgroup analysis based on cancer type was conducted. Thus, more studies might be performed in different OC subtype. Third, many factors could affect prognosis. In the eligible studies, we incorporated lots outcomes with the form of univariate survival analysis. Therefore, studies with multivariate survival analysis should be carried out in the future studies. Fourth, the study was confined to literatures written in English, so language bias could not be ruled out.

In conclusion, our study clarified that c-erbB-2 overexpression was significantly correlated with the poor prognosis in OC patients. In addition, c-erbB-2 overexpression was associated with the following clinicopathological features of OC patients: occurrence risk, gender, lymph node metastasis, and differentiation grade.

Author contributions

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